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EXAMINER	
SCHNIZER, HOLLY G	
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7

Please find below and/or attached an Office communication concerning this application or proceeding.

FILE COPY

Office Action Summary	Application No. 09/811,132	Applicant(s) ANDERSON ET AL.	
	Examiner Holly Schnizer	Art Unit 1653	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period f r Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *14 March 2001* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disp sition of Claims

4)☒ Claim(s) *1-112* is/are pending in the application.

4a) Of the above claim(s) *1-57 and 75-112* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *58-74* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-112* are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on _____ is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *5* .
4) ☒ Interview Summary (PTO-413) Paper No(s). *7* .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restriction

Restriction to one of the following inventions is required under 35 U.S.C. 121:

I. Claims 5 and 27, drawn to recombinant expression constructs encoding an ANT1 polypeptide, classified in class 435, subclass 320.1.

II. Claims 6 and 28, drawn to recombinant expression constructs encoding an ANT2 polypeptide, classified in class 435, subclass 320.1.

III. Claims 7 and 29, drawn to recombinant expression constructs encoding an ANT3 polypeptide, classified in class 435, subclass 320.1.

Claims 1-4, 8-26, and 30-41 link Groups I-III. These linking Claims will be examined with respect to the subject matter of the Invention of Groups I, II, or III, if one of these Groups is elected.

IV. Claims 44 drawn to ANT1 polypeptide, classified in class 530, subclass 300.

V. Claim 45, drawn to ANT2 polypeptide, classified in class 530, subclass 300.

VI. Claim 46, drawn to ANT3 polypeptide, classified in class 530, subclass 300.

Claims 42-43 and 47-57 link Groups IV-VI. These linking claims will be examined with respect to the subject matter of the Invention of Groups IV, V, or VI, if one of these Groups is elected.

VII. Claim 58-74, drawn to a method of determining the presence of an ANT polypeptide in a sample, classified in class 435, subclass 7.1.

VIII. Claims 75-84 and 104 drawn to a method for identifying an agent that binds to an ANT polypeptide and an assay plate for high throughput screening of candidate agents that bind ANT polypeptide, classified in class 435, subclass 7.1.

IX. Claims 85-103 and 107-111, drawn to an ANT ligand, classified in class 530, subclass 300.

X. Claims 105-106 drawn to a method of targeting a polypeptide to the mitochondrial membrane, classified in class 435, subclass 317.1.

XI. Claim 112, drawn to a method of treatment comprising administering a pharmaceutical composition comprising an ANT ligand, classified in class 514, subclass 2.

The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-III are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the genes encoding ANT1, ANT2, and ANT3 are distinct and encode proteins having different structures, functions, and which are expressed in different tissues. For example, ANT1 is expressed in heart and skeletal muscle; ANT2 appears to only be expressed in neoplastically transformed cells with high glycolytic

rates, in tumors, and tumoral cells; and ANT3 is ubiquitously expressed (Giraud et al. J. Mol. Biol. (1998) 281: 409-418, see p. 409, col. 2; ref. BH in IDS filed 3-16-01 as Paper No. 6). Moreover, while ANT1 and ANT3 export ATP synthesized in the mitochondria to the cytosol, ANT2 appears to translocate glycolytic ATP synthesized in the cytosol, to the mitochondrial matrix (see Giraud et al. p. 413, Col. 2). Because the ANT protein isoforms are expressed in different tissues and have different structures and functions, the polynucleotides encoding them are independent and distinct, one from the other, and could be used for different purposes and have different effects.

The inventions of Groups IV-VI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the ANT1, ANT2 and ANT3 polypeptides are distinct are unrelated for the reasons stated in the preceding paragraph. ANT1, ANT2 and ANT3 proteins have different structures, functions, and are expressed in different tissues. Because the ANT protein isoforms are expressed in different tissues and have different structures and functions, they are independent and distinct, one from the other, and could be used for different purposes and have different effects.

The inventions of Groups I-VI and IX are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the expression constructs and host cells of

Inventions I-III, the polypeptides of Inventions IV-VI, and the ligands of Invention IX have different biological structures and different functions. In addition, subject matter of each Group is not coextensive and thus the search for each would constitute a serious burden upon the examiner. For example, the expression constructs of Group I would require consideration of its use for processes other than the production of the protein, such as nucleic acid hybridization assay and the protein would required searches of literature wherein the protein was isolated from its source rather than recombinantly produced using the polynucleotide. Thus, Groups I-III require considerations which are not required in the search for proteins of Groups IV-VI and Groups IV-VI require considerations which are not required in the search for the polynucleotides of Groups I-III. Likewise, the polypeptides of Groups IV-VI have different functions and are used for different purposes than the ligands of Group IX.

The expression vectors of Groups I-III are unrelated to the methods of Groups VII-VIII and XI. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the expression vectors of Groups I-III are not made by nor used in the protein binding assays of Groups VII-VIII or the method of treatment using an agent that binds ANT of Group XI.

Inventions I-III and X are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially

different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the expression vectors of Groups I-III can be used in a method of making the polypeptides or in hybridization assays, which are materially different processes than the method of targeting the ANT polypeptide to the mitochondrial membrane of Invention X.

The ANT polypeptides of Groups IV-VI are unrelated to the methods of Groups VII and XI. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the polypeptides of Group IV are not made by nor used in the method of screening using an ANT ligand of Group VII or the method of treatment using an agent that binds ANT of Group XI.

Inventions IV-VI are related to the methods of Groups VIII and XI as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the polypeptides of Groups IV-VI can be used in a method of making an antibody or in activity assays, which are materially different methods than the protein binding assays and method of treatment using an ANT ligand of Groups VIII and XI.

The ANT ligands of Group IX are unrelated to the methods of Groups VIII and X. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the ligands of Group IX are not made by nor used in the method of screening using an ANT polypeptide of Group VIII or the method of targeting an ANT polypeptide to the mitochondrial membrane of Group X.

The ligand of Invention IX is related to the methods of Inventions VII and XI as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the ligand of Invention XI could be used in a method of inhibiting the activity of the ANT polypeptides, which is materially different than the method of screening for an ANT polypeptide of Group VII or the method of treatment of Group XI. In addition, the ligand could be used in a method of diagnosis, which is materially different from the methods of screening and treatment of Inventions VII and XI.

The methods of Inventions VII-VIII, X, and XI are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the methods of Inventions VII-VIII, X, and

XI are materially different each from the other because each is practiced with materially different process steps, technical considerations, and reagents and each is practiced to accomplish a distinct goal.

Having shown that these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and recognized divergent subject matter as defined by MPEP § 808.02, the Examiner has prima facie shown a serious burden of search (see MPEP § 803). Therefore, the initial requirement of restriction for examination purposes as indicated is proper.

During a telephone conversation with Stephen Rosenman on June 18, 2003, a provisional election was made without traverse to prosecute the invention of Group VII, claims 58-74. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-57 and 75-112 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Sequence Compliance

The disclosure is objected to because of the following informalities: There are no sequence identifiers for the sequences listed in Figures 1A, 1B, and 2. Sequence information in the drawings must still be included in a "Sequence Listing" and the sequence identifier ("SEQ ID NO:X") must be used in the drawings or the Brief Description of the Drawings (see 37 C.F.R. 1.821 and MPEP 2429, 22nd paragraph). Correction is required.

Claim Objections

Claims 58 and 72 are objected to because of the following informalities: Claims 58 and 72 refer only to the acronym "ANT". The full name of the polypeptide should be given in each independent claim. If desired, the acronym may be given in parenthesis after the full name and any dependent claim may refer to that acronym. For example, claim 58 should read "A method for determining the presence of an adenine nucleotide translocator (ANT) polypeptide". Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 59 recites the limitation "the adenine nucleotide translocator" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 58 only refers to an "ANT" polypeptide. Correction is required.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 60-62 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The claims are drawn to methods of determining the presence of ANT1 (clm. 60), ANT2 (clm. 61), or ANT3 (clm. 62) in a sample using a ligand binding assay. However, the prior art, as evidenced by Stepien et al. (J. Biol. Chem. (1992) 267(21): 14592-14597), teaches that ANT1 is *predominantly* in skeletal and cardiac muscles (but is also expressed in Brain and Kidney) and ANT2 (at low levels) and ANT3 are expressed in all tissues tested (see p. 14594, Table I). Thus, a large number of tissues express at least one adenine nucleotide translocator. Moreover, there are additional ANT isoforms such as ANT4 (see WO 99/07845; ref. AG of IDS of Paper No. 5). The presently claimed method does not have any steps that would allow differentiation between whether the binding of the ANT ligand represents ANT1, ANT2, or ANT3. Therefore, in samples

containing more than one isoform (which would be almost all samples since ANT2 is expressed in all tissues) determination of which ANT isoform was present in a sample could not be determined using the claimed method. In the instant case, undue experimentation would be required to determine the presence of ANT1, ANT2 or ANT3 specifically using the claimed method. Factors to be considered in determining whether undue experimentation is required, are summarized in In re Wands (858 F2d, 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)). These factors include (1) quantity of experimentation, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The nature of the invention

The nature of the invention involves the discovery of atractyloside derivatives having various substitutions at the 6' hydroxyl (see Specification pages 92-122) and their use in methods of detection and purification of adenine nucleotide translocators. The claims involve a method of detecting ANT1, ANT2, or ANT3 in a sample by a binding assay using a ligand to an adenine nucleotide translocator.

The amount of direction or guidance presented

The present Specification provides a generic description of a method of detecting adenine nucleotide translocators but does not teach how to differentiate between which ANT polypeptide (of ANT1, ANT2, ANT3 or another ANT isoform) was detected.

The presence or absence of working examples

The present Specification does not provide any working examples that describe how one would differentiate between whether ANT1, ANT2, ANT3, or another adenine nucleotide translocator was detected.

The state of the prior art and relative skill of those in the art

As evidenced by Brandolin et al. (FEBS LETT (1974) 46(1): 149-153; ref. BC of IDS of Paper No. 5), Bojanovski et al. (Eur. J. Biochem. (1976) 71: 539-548; ref. AM of IDS of Paper No. 5).and Klingenberg et al. (Biochim. Biophys. Acta (1978) 503: 193-210; ref. BJ of IDS of Paper No. 5), it appears that the binding affinity of ANT polypeptides with atractyloside and its derivatives were very well known in the art. Furthermore, it was very well known in the art to use this binding affinity in methods of purification and detection. However, a thorough search of the art did not reveal any teachings of how to use atractyloside and its derivatives to determine which isoform of ANT is in a particular sample. Moreover, a thorough search of the art did not reveal any antibodies or other ANT ligands that are specific for a particular ANT isoform and do not react with the others. Fiore et al. (Biochimie (1998) 80: 137-150; ref. BG in the IDS of Paper No. 5) teach that the sequences for ANT1, ANT2, and ANT3 were well known in the art (see p. 139-142) and were highly similar. Therefore, the level of skill of those in the art would allow expression and purification of the ANT isoforms but would not allow prediction as to whether atractyloside derivatives or any other ligands would have unique interactions with each of the ANT isoforms to allow differentiation between them in a method of detection.

The predictability or unpredictability of the art

Since the interaction and binding characteristics of atractyloside and its derivatives or any other ANT ligand with each of the ANT isoforms was unknown at the time of the invention, it would be highly unpredictable to use the claimed method to determine the presence of any particular ANT isoform in a sample.

Quantity of Experimentation

A large quantity of experimentation would be required to find a ligand that would specifically bind to an individual ANT isoform so as to allow differentiation of which ANT isoform is in a sample.

To practice the instant invention would not require just a repetition of the work that is described in the instant application but a substantial inventive contribution on the part of a practitioner which would involve the discovery of an ANT ligand that would bind specifically to a particular ANT isoform and not to any other ANT polypeptides. It is this additional characterization of each ANT isoform and its ligand, required to practice the claimed method, which constitutes undue experimentation.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 58, 63-66, 71and 72 are rejected under 35 U.S.C. 102(b) as being anticipated by Schultheiss et al. (Clin. Exp. Immunol. (1983) 54: 648-654).

Schultheiss et al. teach a method of determining the presence of an adenine nucleotide translocator from bovine liver mitochondria samples during different steps of its purification. In the purification method, samples containing ANT are contacted with ^{3}H-carboxyatractyloside to allow for binding. Then, during the purification of ANT, the ^{3}H-carboxyatractyloside samples containing the adenine nucleotide translocator bound to the detectable ^{3}H-carboxyatractyloside are detected using the radiolabel thereby allowing the determination of which sample contains the ANT polypeptide. (see pp. 649, lines 19-22). Therefore, Schultheiss et al. meets the limitations of Claims 58 and 72. Carboxyatractyloside used in the method is an atracyloside derivative substituted at the 6' hydroxyl therefore Schultheiss et al. meets the limitations of Claims 63 and 71. The ^{3}H-carboxyatractyloside is detectable because it contains the radiolabeled substituent 3H, therefore, Schultheiss et al. meets the limitations of Claims 64-66.

Claims 58, 63-66, 70, and 72-73 are rejected under 35 U.S.C. 102(b) as being anticipated by Brandolin et al. (FEBS LETT (1974) 46(1): 149-153; ref. BC of IDS of Paper No. 5).

Brandolin et al. teaches a method for isolating an adenine nucleotide translocator (also known as an ADP carrier) by contacting rat liver mitochondria (biological sample suspected of containing ANT) with a succinyl-atractyloside-amino Sepharose

(considered an amine modified atractyloside derivative and ANT ligand) to a period of time to allow for binding, and recovering the ANT polypeptide by contacting the ANT polypeptides with ^{3}H-atractyloside (see p. 149, Col. 1, 2nd paragraph). The atractyloside derivative was covalently bound through an arm of diaminodipropylamine to a Sepharose (solid phase) (p. 152-153). Brandolin's purification method as a whole, is considered to meet the limitations of Claims 72 and 73. The Brandolin et al. method is also considered a method of detecting ANT in a sample and therefore Brandolin et al. meets the limitations of Claims 58 and 63. The succinyl-ATR-amino Sepharose used in the method of Brandolin et al. is considered an atractyloside derivative that is amine modified (p. 150, Fig. 1) and therefore, Brandolin et al. meets the limitations of Claim 70. Present Claims 64-66 are anticipated by Brandolin et al. since the Brandolin et al. method uses [3H]-atractyloside to detect the ANT polypeptide (p. 152, Col. 1).

Claims 58, 63, 70, 72, and 73 are rejected under 35 US.C. 102(b) as being anticipated by Bojanovski et al. (Eur. J. Biochem. (1976) 71: 539-548; ref. AM of IDS of Paper No. 5).

Bojanovski et al. teaches a method for isolating adenine nucleotide translocator (referred to as adenine nucleotide translocase) by contacting rat liver mitochondria (biological sample suspected of containing ANT) with carboxyatractyloside (an atractyloside derivative and ANT ligand) (see Abstract, section 2).The carboxyatractyloside was covalently bound to a solid phase (p. 540, Col. 2). Bojanovski's purification method as a whole, is considered to meet the limitations of

Claims 72 and 73. The Bojanovski et al. method is also considered a method of detecting ANT in a sample and therefore Brandolin et al. meets the limitations of Claims 58 and 63. The succinyl-ATR-amino Sepharose used in the method of Bojanovski et al. is considered an atractyloside derivative that is amine modified (p. 150, Fig. 1) and therefore, Bojanovski et al. meets the limitations of Claim 70.

Claims 58, 63-66, and 71-72 is rejected under 35 U.S.C. 102(b) as being anticipated by Klingenberg et al. (Biochim. Biophys. Acta (1978) 503: 193-210; ref. BJ of IDS of Paper No. 5).

Klingenberg et al. teach a method of isolating adenine nucleotide translocator (referred to as the ADP, ATP carrier) by contacting beef heart mitochondria (a biological sample suspected of containing ANT) with carboxyatractyloside (an atractyloside derivative and ANT ligand) (see p. 193, section 1 and p. 195, Materials and Methods, 2nd paragraph). The isolation method of Klingenberg et al. is considered to meet the limitations of Claim 72. The isolation method of Klingenberg et al. is also considered a method of detecting ANT in a sample and therefore Klingenberg et al. meets the limitations of Claim 58, 63, and 71. Present Claims 64-66 are anticipated by Klingenberg et al. since the Klingenberg et al. method uses [^{35}S]-carboxyatractyloside derivative (detectably substituted at the 6' hydroxyl) to detect the ANT polypeptide (p. 152, Col. 1).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 59 is rejected under 35 U.S.C. 103(a) as being unpatentable over Schultheiss et al. (Clin. Exp. Immunol. (1983) 54: 648-654) in view of Fiore et al. (Biochimie (1998) 80: 137-150; ref. BG in IDS of Paper No. 5).

Schultheiss et al. teach a method of determining the presence of an adenine nucleotide translocator from bovine liver mitochondria samples during different steps of its purification. In the purification method, samples containing ANT are contacted with ^{3}H-carboxyatractyloside to allow for binding. Then, during the purification of ANT, the ^{3}H-carboxyatractyloside samples containing the adenine nucleotide translocator bound

to the detectable ^{3}H-carboxyatractyloside are detected using the radiolabel thereby allowing the determination of which sample contains the ANT polypeptide. (see pp. 649, lines 19-22).

Schultheiss et al. do not teach using the method to detect the presence of a human adenine nucleotide translocator.

Fiore et al. teach the sequences of three isoforms of human adenine nucleotide translocator (Fig. 1, pp. 139-142). Fiore et al. also teach that the adenine nucleotide translocator has been implicated in mitochondrial myopathies in man (p. 146, Col. 2) and suggest that assays to detect ANT in human samples are of interest to those in the art (p. 148, Col. 1, last sentence).

Therefore, it would have been obvious to one of ordinary skill in the art at the time of the invention to use the method of Schultheiss et al. to determine the presence of a human adenine nucleotide translocator in human samples as suggested in Fiore et al. One of ordinary skill would have been motivated to use a method of detecting an adenine nucleotide translocator specifically in human samples (containing human adenine nucleotide translocator) in order to further the understanding of the relationship of ANT to mitochondrial myopathy as suggested in Fiore et al.

Claims 67-69 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schultheiss et al. in view of Fiore et al., Rosenburg (Protein Analysis and Purification: Benchtop Techniques (1996) Birkhauser, Boston, MA, pp. 170-182 and 303-322), and Osman et al. (J. Immunol. Methods (1993) 161(1): 97-106).

Schultheiss et al. teach a method of determining the presence of an adenine nucleotide translocator from bovine liver mitochondria samples during different steps of its purification. In the purification method, samples containing ANT are contacted with ^{3}H-carboxyatractyloside to allow for binding. Then, during the purification of ANT, the ^{3}H-carboxyatractyloside samples containing the adenine nucleotide translocator bound to the detectable ^{3}H-carboxyatractyloside are detected using the radiolabel thereby allowing the determination of which sample contains the ANT polypeptide. (see pp. 649, lines 19-22).

Schultheiss et al. uses radiolabeled atractyloside derivative in the method of detection and does not teach a fluorescently labeled atractyloside.

Fiore et al. teach the involvement of adenine nucleotide translocator in myopathies and suggest the use of fluorescently labeled atractyloside to detect the amount of ANT within the mitochrondria in order to screen for ANT deficiencies (p. 147, Col. 2 and p. 148, last sentence). Fiore et al. state that the fluorescent approach is much more sensitive than the radioactive assay since it requires approximately 100 times less biological material.

Rosenburg teaches that radiolabeling, biotinylating, and fluorescent labeling a ligand of the protein of interest are functionally equivalent means for detecting proteins (section spanning 170-171; see also "Biotin-Avidin System", p. 171-172, "Detection of Radiolabeled Proteins", pp. 176-178, and pp. 178-179). Rosenburg teaches that the various isotopes are functionally equivalent in the detection of proteins using a

radiolabeling method (see p. 177). In addition, how the ligands are bound to the solid phase (covalently or non-covalently) are also functionally equivalent (pp. 303-322).

Osman et al. teach that Eu3+ is a known and widely used type of fluorophore in the detection of proteins. As taught by Osman et al. an Eu3+ labeled polyclonal antibody is available that can be used with a streptavidin-biotin detection system. Thus, Osman et al. demonstrates that Eu3+ is functionally equivalent to other detection systems such as biotin, radiolabeling, other fluorescent labels, etc.

As evidenced by the prior art discussed above, one of ordinary skill in the art at the time of the invention was readily aware of all of the various protein detection systems such as radiolabeling, biotinylating, and fluorescence labeling. Also, as evidenced in the prior art, it was well within the skill of the art at the time of the invention to choose the type of labeling that would suit the particular assay at hand. Therefore, for example, it would have been obvious to one of ordinary skill in the art at the time of the invention to modify the method of Schultheiss et al. by using fluorescently labeled atractyloside derivative as suggested in Fiore et al. One of ordinary skill in the art would have had motivation to use a fluorescent label in methods of detecting the amount of ANT in patients with myopathies because high sensitivity (which the fluorescent label would allow) would be necessary in these particular situations.

Conclusions

No Claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Holly Schnizer whose telephone number is (703) 305-3722. The examiner can normally be reached on Monday through Wednesday from 8 am to 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christopher Low can be reached on (703) 308-2923. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703 308-0196.

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